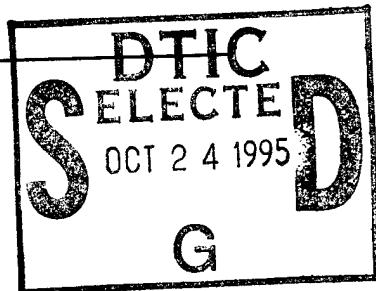


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FOREWORD

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INTRODUCTION

Nature of the Problem

Breast cancer is the most common incident cancer among U.S. women, and the second leading cause of cancer mortality in U.S. women.¹ Increasing numbers of women are employed outside the home. Few studies of breast cancer etiology have addressed occupational and environmental chemical exposures, and many cancer studies of industrial cohorts have excluded women.² Occupational exposure to carcinogens may be of particular concern when the exposures occur during periods of rapid cell division, such as during pregnancy or lactation.²

Only recently has the importance of studying occupational cancer among women workers been recognized.³ Identification of carcinogenic hazards among women workers is of benefit not only to individuals with occupational exposures, but also to the general population, if identification of a hazardous chemical leads to reduction of environmental exposure.

NIOSH is evaluating breast cancer incidence in two large study cohorts, which have been previously assembled. One of the cohorts includes 9,929 women with exposure to ethylene oxide (ETO), a direct alkylating agent which produces mammary tumors in mice.^{4,5} The other cohort includes over 13,000 women exposed to polychlorinated biphenyls (PCBs), a group of chemicals suspected to be carcinogenic to the breast because of their lipophilic and estrogenic activities. Each cohort represents the largest and best defined female study cohort in the U.S. for the respective exposure.

Background

The incidence of breast cancer in the U.S. has increased in the past two decades.¹ Known epidemiologic risk factors for breast cancer include a family history of breast cancer, early age at menarche, nulliparity or late age at first birth, and later age at menopause.⁶ It has been hypothesized that exposure to chemicals in environmentally contaminated food is related to the increasing incidence of breast cancer.⁷ According to this hypothesis, chemicals that bioaccumulate in fatty tissues and those that are estrogenic are most likely to be associated with breast cancer risk. Many chlorinated hydrocarbons, including tetrachlorodibenzo-p-dioxins, polychlorinated biphenyls and some pesticides are lipophilic and estrogenic to varying degrees. One recent study found elevated PCB concentration in the mammary tissue of patients with breast cancer compared to patients with benign breast disease.⁸ Another study did not find a significant association between serum PCB concentration and risk of breast cancer, but did find a significant association for DDE (a metabolite of DDT).⁹ According to the IARC rating scheme, PCBs are probable human carcinogens¹⁰ with sufficient evidence from experimental animal studies to classify PCBs as carcinogenic, but limited evidence from human studies.

Agents that act directly on DNA, such as radiation and chemical alkylating agents, have also been shown to be carcinogenic in mammary tissue in animal studies and in humans.⁷ Although the chemicals that induce breast cancer in humans are not well-defined, it is reasonable to suspect that chemicals that produce mammary tumors in rodent bioassays may also be breast carcinogens in humans.¹¹ IARC has determined that ethylene oxide is a carcinogen based on limited evidence in humans and sufficient evidence in animals (IARC, 1987).¹⁰ The IARC determination was based primarily on leukemia and brain cancer in animals, and leukemia in humans. However, there was also some evidence of mammary cancer in animals and breast cancer in humans exposed to ethylene oxide.

Purpose and Objectives of Present Work

The study has the following primary objectives:

- a. To evaluate whether exposure to ETO or PCBs is associated with increased breast cancer.
- b. To identify incident cases of breast cancer in the ETO and PCB cohorts and to collect information on exposures and relevant risk factors by questionnaire surveys of living women and the next-of-kin of deceased women.
- c. To determine whether the incidence of breast cancer is elevated in each cohort compared to the general population, controlling for non-occupational factors that may be associated with both breast cancer risk and employment status (i.e., nulliparity, age at first birth).
- d. To evaluate the exposure-response relationship within each cohort, controlling for non-occupational risk factors.
- e. If either study is positive, to provide data for risk assessments to estimate risk in the general population.

Methods of Approach

Given the high survival rates for women diagnosed with breast cancer (>75% for white women and >60% for black women), cancer incidence is a much more sensitive indicator of increased risk than cancer mortality. Longstanding population-based cancer registries are available for only one of the three PCB cohorts, which is located in New York State and three of the 14 ETO plants. Thus, cancer incidence will have to be determined through the use of questionnaires. (Registry matching will be done for the plants in areas covered by population based-registries since this will provide an additional means of identifying cases, particularly for individuals who could not be contacted). The questionnaire approach also allows the

collection of data on non-occupational risk factors, which are required for the full interpretation of the incidence study results.

The analysis of the study requires the use of external referent rates, because neither cohort includes an unexposed internal referent group. However, the use of population-based referent rates is problematic because employed women are likely to differ from the general population with respect to factors such as parity which influence both employment status and risk of breast cancer. We will apply methods developed to estimate the effect of smoking habits in occupational cohorts on lung cancer risk¹². This method will estimate the increased risk expected in the occupational cohort based on differences in their reproductive experience alone. This approach will use risk estimates for particular factors (such as nulliparity) derived from breast cancer case-control studies, and survey data on the distribution of the risk factor in the general population. The conclusions of this analysis will be limited because any estimate of the increased risk expected in the cohort based on their reproductive experience is crude. A second analysis will utilize low-exposed women as an internal comparison group. It will examine whether there is an exposure-response relationship within the cohort. In this analysis, both occupational and non-occupational risk factors will be compared between cases and others in the cohort who did not develop breast cancer. We will analyze the exposure-response relationship using a quantitative dose metric only for the ETO cohort. For the PCB cohorts, we will analyze duration of exposure in high, medium or low exposure jobs.

For both cohorts, data from personnel records has already been coded into a standard computer file containing demographic, and work history information. Vital status was determined though data supplied by the Social Security Administration (SSA), the National Death Index (NDI), the Internal Revenue Service (IRS) and the U.S. Postal Service. For the purposes of the present study, the vital status of each of the cohorts will be updated through the most recent year available in the NDI (currently 1993). It is necessary to update vital status before conducting the incidence study because death certificates will be one source for identification of breast cancer cases and the address of the next-of-kin. In addition, the date of death (from any cause) will be used in the incidence analysis to calculate "person-years-at-risk" for each person in the study.

BODY

Progress to Date

The accomplishments to date have focused primarily on preparation for data collection, particularly the determination of vital status and current mailing addresses for the individuals in each study cohort. The activities have included:

- Ascertainment of vital status and current mailing addresses. The primary focus of the first year of this project was vital status determination and address tracing for living cohort members and next-of-kin of deceased members. These tasks have entailed searches of large databases such as the National Death Index (NDI), Internal Revenue Service (IRS), and Social Security Administration (SSA). Another large database, from the Health Care Finance Administration (HCFA) will be searched in August. Current addresses are being solicited from the U.S. Postal Service which keeps records of recent address changes. Vital status has been determined for approximately 70% of the PCB cohort and 95% of the EtO cohort. Current mailing addresses have been identified for approximately 60% of the living members of the PCB cohort and 80% of the living members of the EtO cohort.
- Questionnaire development. The questionnaires (one for living cohort members and one for next-of-kin of deceased members) have been developed and were adapted from those used for a breast cancer study conducted by the National Institute of Environmental Health Sciences (NIEHS). The questionnaires were submitted for approval by the Office of Management and Budget (OMB). Approval was received on July 21, 1995 for a pre-test of the survey instruments among 30 women, but not the full study. It was also recommended by OMB that a Science Advisory Panel be established to review the study protocol, including pretest results, comparison groups, methodology, and study design. OMB's concerns arose as a result of comments to OMB by the companies involved. We are currently establishing the Science Advisory Panel to include independent experts in the area of breast cancer epidemiology, and hope to conduct the pretest and complete the Advisory Panel review by January of 1996. Provided that OMB approval is received at that time, the study should not be seriously delayed.
- Participant contact letters and consent forms. Subject contact documents and informed consent forms have been developed and approved by the NIOSH Human Subjects Review Board (HSRB) and the Human Review and Regulatory Affairs Division of the Department of the Army.
- Survey research contractor. For this study, the contractor will be responsible for mailing the questionnaires, coding, and entering the data, and retrieving medical records for confirmation of reported breast cancer diagnoses. A five-year epidemiology support contract is currently in place. A Statement of Work for the contractor has been drafted

and is under review.

CONCLUSIONS

The primary activities for this first year have focused on establishing vital status and mailing addresses for individuals in the two study cohorts, and seeking OMB approval for the study questionnaires. Work to accomplish vital status and address identification is proceeding in a timely fashion. OMB approval was received for a pretest of the study questionnaires among 30 women. A Science Advisory Panel will be established to review study procedures. Human subjects approvals have been received from both NIOSH and Department of the Army.

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